recapitulated in biophysical studies and could also affect sister kinetochore separation. Regardless of the actual mechanism, the novel finding that a chromatin-based force helps establish the formation of the metaphase spindle is likely to have important implications.

Chromatin was once thought to be a passive participant in transcriptional regulation, but now the modification and remodeling of chromatin is known to play a highly active role in gene-specific regulation. The discovery of elastic chromatin at the spindle [2] suggests that modification and remodeling of chromatin may also play an important role in regulation of chromosome segregation and checkpoint function. Studies in both yeast [10] and human cells [11] have provided evidence that ATP-dependant chromatin remodeling complexes have a direct role in chromosome segregation. Mutations of the yeast RSC complex, for example, impair chromosome segregation [10]. This defect appears to be caused by a defect in RSC mutants depositing cohesin along chromatid arms [12,13]. Whether RSC or other ATP-dependent chromatin remodeling complexes directly affect the resistance of pericentric chromatin to extension is now open for debate. For example, RSC and SWI/SNF complexes generate significant force when disrupting DNA-histone interactions [14], and this force could be harnessed to assist microtubule-based motors.

Covalent modification of pericentric chromatin also influences the fidelity of chromosome segregation [15]. These modifications may directly or indirectly influence the resistance to spindle elongation caused by chromatin. Biophysical studies of acetylated nucleosomes suggest that their stability is compromised [16], such that they may provide less resistance to outward forces on sister kinetochores. Finally, tension felt across centromeres is an important mechanical cue that silences the spindle assembly checkpoint [17]. These new data raise the intriguing possibility that chromatin stretching is monitored by checkpoint signaling mechanisms to determine when to initiate anaphase.

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Invertebrate Neurobiology: Sensory Processing in Reverse for Backward Walking

Humans and many other animals can readily walk forward or backward. In insects, the nervous system changes the effects of sense organs that signal forces on a leg when the direction of walking is reversed.

Sasha N. Zill

A person typically walks with little conscious awareness of the complex sequence of contractions of leg muscles that generate support and propulsion. Humans and many other animals can also rapidly and gracefully reverse the direction of walking. Changing direction when walking is more complex than when driving a car, where merely shifting a gear runs the engine in reverse. In walking forward, a leg is lifted and pulled forward in the swing phase, then placed down on the substrate and pulled back in stance (Figure 1A). In backward walking, a leg is lifted and pulled back in swing, then put

down and pulled forward in stance [1]. This implies that muscles that move the leg forward (leg protraction) or backward (retraction) are active during different phases of the step cycle in walking forward versus walking backward. How does the nervous system generate and adapt walking in different directions? Insight into this problem has been gained from recent studies by Akay *et al.* [2] which have shown that the effects of sense organs that monitor forces acting upon a leg in stick insects are changed when the walking direction is reversed.

Stick insects can readily walk forward or backward, a very useful ability for animals that reside on and mimic tree branches [3,4]. The muscle contractions that occur in walking in stick insects, like those in many other animals, are thought to be produced by circuits of neurons in the nervous system that form central pattern generators [5]. Part of the nervous system containing pattern-generating circuits can be isolated and, in many cases, will produce rhythmic bursting in motor nerves, similar to that seen in walking, after application of neurotransmitter substances or mechanical or electrical stimulation. Akay *et al.* [2] were able to activate walking in stick insects by touching the body or by applying the muscarinic agonist pilocarpine. Although pattern generators for walking can function in isolation, feedback from sense organs in the legs that monitor movements and forces has strong effects on the level and timing of muscle activities [6–8].

In stick insects, as in other invertebrates, many leg sense organs are organized in groups that are individually identifiable. Akay *et al.* [2] precisely activated receptors that monitor forces on the legs, called campaniform sensilla, to produce sensory signals that mimicked sudden increases in load [9,10]. The campaniform sensilla of the stick insect that are concentrated on a small leg segment (called the trochanter) have been shown to elicit load compensatory reflexes in the protractor and retractor muscles in animals at rest [11]. The effects of the sensilla have also

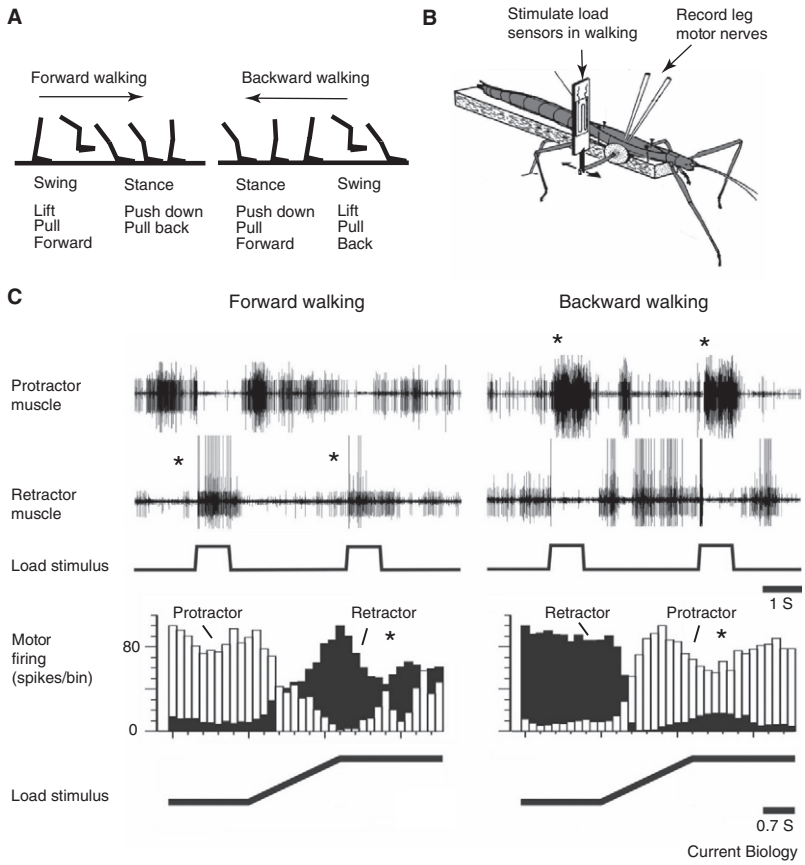

Figure 1. Sensory feedback in backward walking.

(A) Patterns of muscle activity are changed when walking backward. When the foot is on the ground (stance phase) the leg is pulled back (retracted) to provide propulsion in forward walking but pulled forward (protracted) in backward walking. (B) Sense organs of the stick insect leg can be selectively stimulated in walking in a preparation that has five legs free to move. Forces are applied to the sixth leg while the animal walks on a slippery glass surface. (C) Stimulation of the force receptors, mimicking a sudden increase in load, produce activation (indicated by the asterisk) of the retractor muscle in forward walking and the protractor muscle in walking backward. The effects of the sense organs change with the direction of walking so that they excite muscles that are active in the stance phase. (Panels A, B and C adapted from [1], [11] and [2], respectively.)

been studied in animals that were walking on a treadmill by using a preparation in which five legs were free to move and the sixth leg was held in what was effectively a prolonged stance phase (Figure 1B). Forces applied to the leg stump specifically excited the trochanteral load sensors.

How does the feedback system change when animals walk backward? Akay *et al.* [2] took advantage of an interesting observation made by Ulrich Bässler and colleagues [3], that the hind legs of stick insects preferentially walk backward after decapitation or following removal of the front and middle legs. In contrast, the front and middle legs walk forward when isolated. This provided the opportunity to study the effects of sensory signals of load in different segments that walked in different directions. Load stimuli were first applied in preparations in which all legs had been removed except one. In the front and middle legs, stimulation of load sensors increased activity in the retractor muscle and decreased or terminated protractor firing. These effects closely resembled the transition from the swing to stance phases in forward walking [12]. Sensory stimulation had the opposite effect in muscles of the hindleg: retractor activity was terminated and protractor activity was initiated, similar to the transition from swing to stance if the animal was walking backward.

Do the load receptors have similar effects in freely walking animals? Are the effects specific to the segmental (front, middle or hind) leg or do they depend upon the walking direction? To answer these questions, the receptors were stimulated in animals that were more intact and walking on a glass plate. In all legs, the effect of increased load was directly correlated with the direction of walking (Figure 1C): retractor motor neurons were excited in forward walking and protractor firing was initiated or enhanced if the animal was walking backward. Experiments in which the receptors were ablated confirmed that the trochanteral campaniform sensilla were responsible for these effects.

These studies therefore demonstrated that the nervous system modulated the effects of load receptors when the walking pattern generator was activated, depending upon the direction of locomotion. These changes allow the receptors to fulfill the same function of enhancing muscle activities in stance, even when different groups of muscles were activated in different directions of walking.

Are similar mechanisms found in other animals or in humans? Pattern-generating circuits are thought to be inherent in the design of the nervous system of animals but, until recently, humans were viewed as an exception, as they 'learned' to walk. Experiments on human infants by Jaynie Yang and colleagues [13,14] have changed this view. They showed that infants who are not able to walk on their own can walk remarkably well on treadmills if their body weight is supported. The patterns of muscle activities in infants closely resembled those seen in adults, suggesting that the nervous system was able to 'walk' at birth but that infants had not yet learned to maintain their balance while walking.

Some experiments on infants closely parallel those on stick insects [14]. Infants that are supported can also walk in different directions, including walking backward. Analysis of walking patterns showed that many of the parameters of walking — the relationship between stance and swing phase durations and cycle duration — were the same across a range of speeds regardless of the direction of stepping. These findings suggest that there is considerable sharing of neural circuitry for the generation of forward and backward walking. Perturbations during walking produced effects in leg muscles that depended upon the direction of walking. For example, unloading of a leg produces initiation of swing in many animals. Pang and Yang [14] found that, in any direction of walking, the most effective sensory input to promote initiation of swing was perturbation in a direction opposite that of progression. The nervous system was able to modulate the effects of sensory inputs according to the direction of walking — the same effect that was observed in stick insects.

How does the nervous system change the effects of sensory feedback? In all nervous systems there are parallel pathways that process sensory information that could be selectively enhanced or inhibited when the direction of walking is changed [7]. These mechanisms probably do not represent simple switches but instead can allow for changes in the timing of motor firing and the rhythm of walking. Another mechanism to change the effects of sensory inputs could be through synapses that are made upon sensory endings within the nervous system (presynaptic inhibition) [15,16]. The findings in stick insects point the way for future studies that could evaluate these mechanisms [17] and clarify how pattern generators for walking produce a variety of behaviors by modulating connections between neurons.

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